DETAILED ACTION

The amendments and arguments filed Sep. 28, 2010 are acknowledged and have been fully considered. Claims 9 and 11-19 are now pending. Claims 1-8 and 10 are cancelled; claim 9 is amended; claim 11 is withdrawn; claim 19 has been added. Claims 9 and 12-19 are now under consideration.

Information Disclosure Statement

Applicants request consideration of the references filed Sep. 6, 2006. However, a review of the file wrapper indicates that no SB/08 form listing these references was filed. If applicants wish these references to be considered, it is requested that they file form PTO/SB/08 properly listing these references for consideration.

OBJECTIONS/REJECTIONS WITHDRAWN

The objection to the specification (i.e. the domestic priority claim) is withdrawn, in light of the amendments to the specification filed 9/28/10.

The rejection of claims 9 and 12-18 under 35 U.S.C. 112, 1st paragraph, lack of enablement, is withdrawn in light of the claim amendments (SEE DISCUSSION BELOW).

The rejection of claims 9 and 12-18 under 35 U.S.C. 102(b) is withdrawn in light of the claim amendments.

OBJECTIONS/REJECTIONS MAINTAINED

The rejection of claims 9 and 12-18 under 35 U.S.C. 112, 1st paragraph, lack of written description, is maintained as discussed below.

The double patenting rejections of record have been maintained as no action regarding these rejections has been taken by applicants at this time.

Claim Rejections - 35 USC § 112 (1st Paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claims 9, 12-18, and new claim 19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, the claims encompass *any* dual antagonist for the 5-HT_{2B} and 5-HT_7 receptor (i.e. both single compounds having dual activity and separate compounds administered together), but applicants were clearly not in possession of any and all such compounds at the time of filing.

Regarding the requirement for adequate written description of chemical entities, Applicant's attention is directed to the MPEP §2163. In particular, *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089, 118 S. Ct. 1548 (1998), holds that an adequate written description requires a precise definition, such as by structure, formula, chemical name, or physical properties, "not a mere wish or plan for obtaining the claimed chemical invention." *Eli Lilly*, 119 F.3d at 1566. The Federal Circuit has adopted the standard set forth in the Patent and Trademark Office (PTO) Guidelines for Examination of Patent Applications under the 35 U.S.C. 112.I "Written Description" Requirement ("Guidelines"), 66 Fed. Reg. 1099 (Jan. 5, 2001), which state that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics," including, *inter alia*, "functional characteristics when coupled with a known or disclosed correlation between function and structure..." *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 316, 1324-25 (Fed. Cir. 2002) (quoting Guidelines, 66 Fed. Reg. at 1106). Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient. MPEP §2163. However, if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is “not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence.” MPEP §2163.

The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Univ. of Rochester v. G.D. Searle*, 69 USPQ2d 1886, 1892 (CAFC 2004). A description of what a material does, rather than of what it is, usually does not suffice to provide an adequate written description of the invention. *Univ. of Cal. V. Eli Lilly*, 119 F.3d 1559, 1568 (Fed. Cir. 1997). Furthermore, to the extent that a functional description can meet the requirement for an adequate written description, it can do so only in accordance with PTO guidelines stating that the requirement can be met by disclosing "sufficiently detailed, relevant identifying characteristics," including "functional characteristics when coupled with a known or disclosed correlation between function and structure." *Univ. of Rochester v. G.D. Searle*, 69 USPQ2d 1427, 1432 (DC WNY 2003).

In paragraph [0044] of the published application, applicants disclose a subgenus of compounds (related by the core fluorine structure) that are asserted to have the claimed dual 5-HT_7/5-HT_{2B} antagonism properties. Only 8 compounds, all of which have the same core fluorine structure, are actually disclosed as having the claimed receptor binding profile (see par. [0148]). The claims are in no way limited to this subgenus of compounds. Applicants have failed to provide sufficient description of the various compounds as recited in instant claim 9 that would provide adequate written description of the compounds encompassed by the scope of the claim. Adequate written description requires a precise definition, <u>such as by structure, formula, and chemical name, in combination with physical properties</u>. In the present case, other than the <u>specific</u> derivatives mentioned (see pars. [0044] and [0148]), the disclosure fails to

describe the claimed compounds in a manner that complies with the written description requirement of 35 U.S.C. 112, 1st Paragraph.

Response to Arguments

Applicants' arguments have been fully considered but are not persuasive. Applicants argue that the disclosure at pars. [0022], [0031], and [0032] satisfies the written description requirement, and argue that the examiner has not provided evidence or reasons why a person skilled in the art would not recognize written description support (response, p. 8).

Neither the paragraphs to which applicants refer nor the specification as a whole provides proper written description support for the claims, as incorrectly asserted by applicants. The 3 paragraphs cited by applicants (presumably those of the published application) refer, broadly to ANY compound having dual antagonist for the 5-HT_{2B} and 5-HT_7 receptors. Applicants have claimed, in tremendously broad functional language, ANY compound having certain receptor binding properties. Functional language is generally only sufficient to fulfill the written description requirement "when coupled with a known or disclosed correlation between function and structure..." *Enzo Biochem, Inc. v. Gen-Probe Inc* (emphasis added). Yet functional language is what applicants point to as their alleged written description support (e.g. pars. [0022] and [0032]). The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Univ. of Rochester v. G.D. Searle*, 69 USPQ2d 1886, 1892 (CAFC 2004). No one can visualize or recognize the identity of the limitless scope of compounds that the instant claims encompass because applicants have not

provided *sufficient* correlation between structure and function for the full scope of the claims for such visualization to be even remotely possible.

Furthermore, it is also recognized that for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim and/or the genus must be sufficiently detailed to show that applicant was in possession of the claimed invention ***as a whole*** (see *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555 (Fed. Cir. 1991)). Otherwise, as stated by the court in *Ariad Pharmaceuticals, Inc., v. Eli Lilly and Company* (Fed. Cir. 2010), "a generic claim may define the boundaries of a vast genus of chemical compounds, and yet the question may still remain whether the specification, including original claim language, demonstrates that the applicant has invented species sufficient to support a claim to a genus. The problem is especially acute with genus claims that use functional language to define the boundaries of a claimed genus. In such a case, the functional claim may simply claim a desired result, and may do so without describing species that achieve that result. But the specification must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus." (emphasis added)

Thus, as discussed by the *Ariad* court, "the level of detail required to satisfy the written description requirement varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology". In particular, the court identifies "a number of factors for evaluating the adequacy of the disclosure, including 'the existing knowledge in the particular field, the extent and content of the

prior art, the maturity of the science or technology, [and] the predictability of the aspect at issue." As such, "the number of species that must be disclosed to describe a genus claim… necessarily changes with each invention, and it changes with the progress in a field." In this case, applicants have disclosed only 8 working examples, all of which are highly structurally related by a single fluorine core. Where is the written description support for compounds having any other core structure? Applicants can point to none. Where do applicants provide a disclosure of structural characteristics that a skilled artisan could use to correlate to the function of the genus claimed? Indeed, no such guidance is present. This is particularly problematic in this case because of the tremendous breadth of the claims and the immature field of the invention (i.e. single compounds possessing selectivity for inhibition at two distinct receptors), few of which are actually known. Thus, as in *Ariad*, applicants would need to provide a correspondingly higher number of representative examples of diverse chemical structure to show possession of the entire genus. However, applicants claims encompass any and all such compounds, while only a single core structure is disclosed.

Applicants cite five ways that written description can be satisfied (i.e. elements [1]-[v] on p. 9 of the response.

However, what is notably lacking in the specification is any correlation between structure and function that would be sufficient to provide written description of the entire genus instantly claimed. Beyond the limited subgenus of compounds which have actually been invented and disclosed, no discussion of structure or other chemical properties exists (i.e. not functional language) in the specification that provides any of

the written description elements [ii]-[v] for any other compounds. Regarding element [i], the 8 compounds disclosed as having the claimed function are insufficient to provide a representative number of species for the full scope of the claims. Moreover, ALL of the compounds disclosed, which may or may not have the claimed function, are based on the single fluorene core structure, and thus cannot be considered proper written description support for any other class of compound. The written description rejection is maintained because applicants have provided insufficient examples and insufficient correlations between function and structure *for the full scope of the claims*.

It is noted that the examiner suggested incorporating applicants' elected species into the base claim which would overcome the written description issue (see interview summary dated 8/30/10) and move the case towards allowance, but applicants have not done so.

Claim Rejections - 35 USC § 112 (1st Paragraph)

Scope of Enablement

Response to Arguments

The scope of enablement rejection of claims 9 and 12-18 is **withdrawn** herein due to applicants' claim amendments. However, part of applicants' remarks regarding this rejection warrant comment. On p. 11 of the response, applicants assert that,

> "...treatment or inhibition of migraines according to the claimed method includes administering a composition to a symptomatic or an asymptomatic patient to reduce the frequency of attack or severity of pain. See Specification at [0031] and [0074]. Applicants also understand that "treatment or inhibition of migraines," as set forth in the amended claims refers to the partial or complete treatment or inhibition of migraine in a migraine patient or a patient who has been diagnosed to be migraine or in whom periodical attacks of migraine occur. Specifically, inhibition includes the complete inhibition of attack and cessation of pain."

The examiner cannot agree with applicants' interpretation of what the claims encompass. For example, administration of the claimed antagonist(s) to an asymptomatic patient prior to the development of an actual migraine, combined with applicants' assertion of "complete inhibition" is tantamount to "prevention of migraines", which was the issue that formed the basis of the (now withdrawn) scope of enablement rejection. It is noted that the examiner never stated that applicants were enabled for "complete inhibition" of anything. In fact, if the scope of the instant claims could actually be construed to include "complete inhibition" (which it cannot), the rejection would be maintained. However, no support, whether by the description in the specification or by data provided therein, exists in the instant application for "complete inhibition" of migraines or symptoms thereof in any sense. Since applicants have no support for this language, and since it is not claimed, the claims cannot possibly encompass "complete inhibition" as asserted by applicants. Thus, the scope of enablement rejection is withdrawn. However, if applicants were ever to amend the application to encompass "complete inhibition", the scope of enablement rejection would be reinstated because the disclosure is not enabled for this language.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 9 and 12-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over CRAIG (U.S. 6,440,988; Issued Aug. 27, 2002) in view of PARSONS (Parsons, A. A., *et al*. Curr. Opin. Pharm. 2003. 3; 73-77; on IDS dated 9/25/09), TERRÓN (Terrón, J. A. Eur. J. Pharm. 2002. 439; 1-11), MYLECHARANE (Mylecharane, E. J. J. Neurol. 1991. 238 (Suppl. 1); S45-S52), and AUDIA (U.S. 5,886,004; Issued Mar. 23, 1999).

1. Craig discloses a method of treating a subject comprising administering a therapeutically effective amount of an antagonist that binds to both 5-HT_7 and 5-HT_{2B}

receptors (abstract; col. 4, lines 40-41). Craig teaches that the 5-HT_7/5-HT_{2B} antagonist binds the 5-HT_7 receptor and the 5-HT_{2B} receptor with an affinity at least 10-fold higher than the affinity with which it binds each of the human α_1($_{1A}$ or $_{1B}$) adrenoceptor, dopamine D_2 receptor, 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_3, 5-HT_4, and 5-HT_6 receptors (col. 4, lines 50-56; col. 8, lines 10-14 and 36-46). Thus, Craig teaches the only active step of the instantly claimed method (i.e. claim 9), and teaches a pharmacokinetic profile that matches that claimed exactly except for being silent as to the affinity of the compounds at the M_1 (muscarinic) receptor. Nonetheless, given that the antagonists fit the instantly claimed profile at every other receptor claimed, it is highly likely that these compounds inherently have a higher binding affinity at the 5-HT_7 and 5-HT_{2B} receptors than at the M_1 receptor as well. Moreover, the instant claims encompass receptors from any species of animal (i.e. not just human). Thus, in absence of evidence to the contrary, the compounds disclosed by Craig inherently have a higher binding affinity at the 5-HT_7 and 5-HT_{2B} than at least one other M_1 receptor from a non-human animal.

2. Craig does not teach treating or inhibiting migraines using the disclosed antagonist. However, such would have been obvious to a skilled artisan at the time of the invention.

3. Craig teaches that compounds that antagonize the actions of 5-HT at both 5-HT_7 and 5-HT_{2B} receptors act to diminish the neurogenic impulses which initiate smooth muscle contraction (col. 3, lines 11-15; col. 4, lines 30-34; col. 20, lines 44-45). It is noted that smooth muscle contraction (e.g. vasoconstriction) has been implicated in the

etiology of migraines (see Terrón and Mylecharane below). Furthermore, the 5-HT_7 and 5-HT_{2B} receptors are well-known to be involved in the etiology of migraines.

4. For example, Terrón teaches that the 5-HT_7 receptor is involved in the onset of migraine (title; abstract), and suggests the use of antagonists at this receptor for migraine prophylaxis (p. 4, 2nd col.; p. 7, 2nd col.; conclusion). Terrón additionally teaches the involvement of 5-$HT_{2B/2c}$ receptors (p. 3, 2nd col. to p. 4, top of 2nd col.; conclusion). Additionally, Mylecharane teaches that 5-HT has been implicated in the pathophysiology of migraine, and drugs with 5-HT_2 receptor blocking activity are recognized as being clinically effective in migraine prophylaxis (title; abstract). Mylecharane teaches that although these drugs have activity at histamine H_1 muscarinic cholinergic, α_1-adrenergic, α_2-adrenergic and dopamine receptors, drugs which are selective for these non-5-HT receptors appear to be of no benefit in migraine (abstract). Thus, one would know that an antagonist for migraine treatment should be selective over these receptors to avoid unwanted biological effects mediated by these receptors, just as those of Craig. Mylecharane teaches that cranial vasoconstriction is mediated by 5-HT_2 receptors, and that this effect is relevant to migraine (abstract; Table 1; p. S46, 1st col. last par.). Parsons also teaches a role for both 5-HT_7 and 5-HT_{2B} receptors in triggering migraine, and suggests inhibition of these receptors as migraine prophylaxis (p. 75 2nd col.). Likewise, Audia discloses novel compounds selective for the 5-HT_{2B} receptor (title; abstract). Audia teaches that these compounds are useful for the treatment of migraine as well as bladder dysfunction (col. 4, lines 5-19; claim 20).

5. In light of these teachings, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to use a 5-HT_7/5-HT_{2B} receptor antagonist as taught by Craig to treat migraine. One would have been motivated to do so with a high expectation of success since a large body of literature (only some of which is cited above) exists that establishes the utility of 5-HT_7 and 5-HT_{2B} receptor antagonists as useful treatments for migraine. In particular, Audia directly recognizes the utility of such compounds for the treatment of bladder dysfunction (taught by Craig) *and migraine*. Therefore the use of a dual antagonist as taught by Craig to treat migraine is rendered obvious.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

U.S. Patent Application No. 11/997,956

Claims 9 and 12-19 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 22 of copending Application No. 11/997,956. Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of the '956 claims

anticipates or renders obvious that of the instant claims. The difference between the two claim sets is that the '956 claims do not recite the receptor binding affinities instantly recited. However, as stated above, the receptor binding affinities are merely an inherent property of the compounds recited in the '956 claims, which encompass the compounds described in the instant application to have these attributes along with many compounds that are no more than close structural analogues thereof, and would therefore be expected to have the same properties. Thus, the entire scope of the instant claims is anticipated or rendered obvious by the '956 claims.

Response to Arguments

Applicants' arguments have been fully considered but are not persuasive. Applicants argue that the conflicting claim is withdrawn in the copending case, and that a terminal disclaimer would be premature (response, p. 13).

The status of a copending claim is irrelevant to the issue of double patenting. As long as the conflicting claim is pending (i.e. not cancelled), an ODP issue exists. The rejection is maintained since no action has been taken by applicants at this time.

Summary/Conclusion

Claims 9 and 12-19 are rejected; claims 1-8 and 10 are cancelled; no claims are currently allowable.

Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kevin S. Orwig whose telephone number is (571)270-5869. The examiner can normally be reached Monday-Friday 7:00 am-4:00 pm (with alternate Fridays off). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau can be reached Monday-Friday 8:00 am-5:00 pm at (571)272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/KSO/

/Sharmila Gollamudi Landau/
Supervisory Patent Examiner, Art Unit 1611